Professor Goodsir
with the Author's
compliments

THE

PRESENT ASPECT

OF THE DOCTRINE OF

CELLULAR PATHOLOGY:

A LECTURE DELIVERED AT AN EVENING MEETING OF THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH,

27TH FEBRUARY 1863.

BY

WILLIAM TURNER, M.B.LOND., F.R.C.S.E., F.R.S.E.,

SENIOR DEMONSTRATOR OF ANATOMY IN THE UNIVERSITY OF EDINBURGH.

EDINBURGH: PRINTED BY OLIVER AND BOYD.

MDCCCLXIII.

c

REPRINTED FROM THE EDINBURGH MEDICAL JOURNAL, APRIL 1863.

CELLULAR PATHOLOGY.

Since the period when the higher powers of the compound microscope began to be applied to the investigation of morbid processes and the determination of the structure of tumours and other new formations, pathologists have been familiar with the fact, that cells and nuclei, in various stages of development and modifications of shape, enter largely into the composition of the new products of disease. The recognition of this very important structural fact must be regarded as the starting-point of the doctrine of Cellular Pathology.[1]

But whilst all, I suppose, are prepared to grant the cellular nature of morbid growths, and the influence exercised by nucleated cells in pathological processes, yet there has been much difference of opinion respecting the source from whence these cells arise. To attempt to follow out on this occasion the mode of origin of all the structures, and to discuss all the changes which may take place in disease of the textures, would indeed occupy far more time than could reasonably be allotted to a single lecture; and our information on many points is, perhaps, not as yet sufficiently definite to enable one to state with precision many of the events which do occur. But I have thought that it might not be uninteresting to many now present, and quite within the compass of the time placed at my disposal, to give a brief account of some of the many careful and beautiful observations which have within the last few years been recorded on the mode of origin of the corpuscles which occur in such quantities in the so-called inflammatory exudations, and of the formation of the corpuscles of pus, cancer, and tubercle.

And, indeed, it is not inappropriate that we in this place should inquire into the progress which has of late been made in the development of our knowledge of this department of our subject; for it was in

[1] It was by Johannes Müller and his pupils Schwann and Henle, nearly thirty years ago, that this great step was made in pathology.

this city, nay, within the walls of this very College, now some twenty years ago, that the present learned and distinguished Professor of Anatomy in the University, who at that time occupied the post of Conservator of the Museum of our College, by pointing out the share which the existing cells and nuclei of the textures take in the production and progress of various morbid processes and in the formation of new structures, offered the first satisfactory evidence of, and gave the clue to, the correct conception of the process.[1]

But whilst claiming for our own countryman the credit of having adduced the first illustrations of the share taken by the pre-existing cells and nuclei of the textures in the production of various morbid processes, and their increase in these processes by endogenous multiplication,[2] we must at the same time accord to Professor Virchow of Berlin the merit of having, by the vigour of his writings, by his own numerous observations, and the investigations which he has stimulated his pupils to perform, more prominently brought forward the germinative changes which occur in various textural diseases, and in the inflammatory process, and greatly extended their applicability. His Archiv abound with papers by himself and his pupils, from which much information may be derived; and in his Lectures on Cellular Pathology he has placed within our reach a clear and systematic exposition of the subject.

Before proceeding to discuss the evidence which has been advanced of the mode of origin of morbid cell-structures, it may be advisable to say a few words respecting the leading opinions which have been entertained of the manner of development of the cells in the normal formation of the tissues. If we turn to the standard works on the structure and development of the textures, published only a few years ago,[3] we shall find it stated that, in the usual course of development, cells may arise in one or other of two ways:—

1. By the intermediation of and descent from other cells.
2. By the free formation of cells in an amorphous or slightly granular blastema.

[1] These proofs were advanced by Mr Goodsir in courses of lectures delivered in the College in the summer of 1842, and in the winter 1842-43. The leading facts were afterwards published in the Anatomical and Pathological Observations (Edinburgh, 1845). In a paper "On the Origin and Development of the Diseased Condition of Peyer's Glands, which occur in some forms of Continued Fever," read before the Medico-Chirurgical Society of Edinburgh, February 1842, and published in the London and Edinburgh Monthly Journal, April 1842, and in a paper on "The Structure of the Human Kidney," in the same volume, p. 474, additional illustrations of the share taken by nucleated cells in pathological processes and in the development of new cells are adduced. It is interesting also to note, that the examination of the diseased condition of Peyer's patches was one of the first circumstances which led Virchow to entertain his present conceptions of the mode of origin of new cell-formations (Cellular Pathologie, Lect. 18).

[2] Anat. and Path. Obs., pp. 13, 17, 68, 108, pl. i. figs. 1, 2, 3, 13.

[3] Dr Sharpey's Introduction to Quain's Anatomy, 1848; Kölliker's Handbuch der Gewebelehre, 1852.

The first mode of cell-formation is illustrated by the process of endogenous cell-multiplication, originally pointed out in the early stages of cell-development in the ovum by Martin Barry, and since repeatedly confirmed by numerous subsequent observers. The multiplication of cells by division—fissiparous multiplication—as in the early stages of formation of the blood corpuscles, also comes under this head.

The second mode of cell-formation is that which, originally advanced by Schleiden and Schwann, was adopted, with some slight modifications, by Henle.[1] It constitutes the well-known *cell-theory* of those writers. According to this theory, by a process analogous to that of crystallization, a few granules aggregate together in a fluid blastema, either at once to form the nucleus of a cell, or else at first to form a nucleolus, around which a nucleus is afterwards produced. Around this nucleus matter is then gradually deposited, until at length a cell is formed. This theory of the free formation of cells in a blastema for some years held its ground as the principal method by which new cells arose during the normal development of the textures.

The progress of investigation has, however, gradually caused physiologists to give up first one and then another of the supposed instances of spontaneous, exogenous, free cell-formations, which were originally adduced as examples of the process, until at length the theory of free cell-formation has ceased to hold a place in our conceptions of normal histogenesis;[2] so that the doctrine of the development of normal cells by descent from pre-existing cells is almost universally admitted.

But though banished from the field of normal histogenesis, the mode of origin of cells in a fluid blastema by a free spontaneous generation is still considered by some to be the one which prevails in pathological cell-formations; and the well-known inflammatory exudation-corpuscles, and the cells of pus, cancer, and tubercle, are regarded as produced in this manner. In the pathological processes which lead to the production of these corpuscles, the exudation, which is not unfrequently poured out from the bloodvessels amongst the textures, is looked upon as the equivalent of that fluid blastema in which Schwann supposed the spontaneous cell-formation to occur in the course of normal development. And as small granules and visible molecules are often seen in the exudation, the cells are supposed to arise from them. That an exudation may take place amongst the textures in inflammation is evident enough

[1] Although Schleiden is usually considered as a supporter of the theory of free cell-formation, yet that distinguished botanist fully recognised that the new cells of plants were never formed except within those already existing. In support of this statement, I may refer to his Principles of Botany, pp. 103, 257, 465, 527.

[2] The change which has taken place in the statements of physiologists on this matter may be well seen by comparing Kölliker's Handbuch, edition 1852, with his English edition 1860;—see, also, Leydig's Histologie, p. 9. 1857.

in many cases, as in phlegmonous erysipelas, the effusion into the sac of an inflamed serous membrane, and the exudation on the surface of a stump after amputation. But that the cell-forms met with in such exudations are produced in them by any precipitation or aggregation of visible molecules is a mere hypothesis, based on no satisfactory observations, and opposed to the whole course of embryological and histogenetic inquiry.

The frequent existence of multitudes of small granules and visible molecules in such exudations as the fluid of a pleurisy, or a pericarditis, has apparently led those pathologists who look for the formation of cell-forms by the mere aggregation of such particles to the conclusions they have arrived at. But the more probable explanation of the signification of these particles is to regard them not as histogenetic in their office, but as histolytic, *i.e.*, as products of the disintegration of texture, not as agents in its production. And that the cells both of normal and pathological structures may undergo such a degeneration into granules was long ago conclusively established by the observations of Reinhardt,[1] and has been satisfactorily confirmed by numerous subsequent observers.[2]

And here I may remark how important it is that, in our endeavours to trace the mode of origin of the cell-structures met with in pathological new formations, we should not lose sight of the principles which regulate the development of the normal textures. Undoubtedly, in the two cases the results of such formations vary greatly: in the one being useless and purposeless as regards the wants of the economy, in the other ministering to its requirements. But the principles which regulate the development of a texture, whether it be normal, or whether it be pathological, are the same. The proposition *Omnis cellula e cellulâ* applies alike to each. Thus, whilst all *à priori* reasoning, from the basis of normal development, points to the descent of these pathological structures from previously-existing textural elements, yet in this, as in any other question amenable to careful observation and experiment, we ought not to rest satisfied with such a form of reasoning, but apply ourselves to the investigation of the subject. I shall now, therefore, proceed to the consideration of the evidence, founded on numerous examinations, and recorded by various observers, which has been advanced in support of this doctrine of continuous cell-development.

To render such a doctrine at all admissible, it is necessary that its originators and supporters be in a position to show that in all the textures and organs in which the formation of the corpuscles of pus, cancer, and tubercle take place, pre-existing cellular and nuclear particles occur.

In many of the textures and organs, as in muscular fibre, cartilage, the grey matter of the nervous centres, and the various forms

[1] Traube's Beiträge, b. ii. 217.
[2] See, especially, Paget's Lectures on Surgical Pathology, p. 380.

of epithelium, such existing cells and nuclei are universally recognised by anatomists, not only in the early stages of development of those textures, but persisting throughout life. In other parts, again, as in bone and nerve fibre, they have not been so generally admitted; but the observations made, now many years ago, by Mr Goodsir,[1] and since confirmed by Donders, Virchow, Kölliker,[2] and Beale,[3] leave no room for doubting the existence of nuclei in the lacunæ of bone; and their presence in nerve-fibres has now been so frequently figured and described by independent observers, that we cannot but accept them.

It is, however, to their existence in the connective tissue that attention has of late years been particularly directed, and this more especially by Virchow. In some forms of connective tissue, indeed, as in that which constitutes the thick skin of the Sun-fish, the cells and nuclei may be seen lying amongst the fibres without the use of any reagent.[4] But, as a rule, before a demonstration of these structures can be effected, it is necessary to add to the texture some reagent, which, by rendering the fibres so transparent as to be almost or entirely invisible, permits the cells or nuclei to be seen. And, in the various forms of connective tissue met with in man and the higher animals, these cells, instead of being round or oval as in the skin of the sun-fish, are variously fusiform and stellate in shape. Anatomists had long been familiar with the fact, that, when acetic acid was added to a portion of tendon or fascia, numerous minute oval bodies, previously concealed by the fibres, came into view, and these were described as the nuclei of the texture;[5] but that these nuclei were enclosed within distinct cells—the connective-tissue corpuscles—and that the cells possessed in many cases a radiated and anastomosing arrangement was not known until Donders,[6] Virchow,[7] and Von Wittich[8] pointed it out. The demonstration of these cells in the connective tissue, their connexions with each other, and their relation to the fibrillated bundles, which thus represent merely a form of intercellular substance, must be

[1] Anat. and Path. Observations, p. 65, 1845.

[2] Microscopic Anatomy, 1860, p. 175.

[3] Gulstonian Lectures, pl. viii. 1861. Mr Goodsir has for many years taught that nuclei exist not only in the lacunæ of bone, but in the delicate cellular membrane which is prolonged along the Haversian canals. The presence of nuclei in the bone-corpuscles I have been in the habit of demonstrating for several sessions to my class, and preparations were exhibited at the lecture.

[4] I have given an account of the structure of the very remarkable skin of this fish in the Natural History Review, April 1862. The cells, or connective-tissue corpuscles, were seen in great numbers lying amidst the fibres, but in no case did I detect a radiated or anastomosing arrangement.

[5] J. Goodsir, Anat. and Path. Obs., p. 1. Reference may also be made to Mr Bowman's article "Muscle" in Todd's Cyclopædia, and to Dr Martin Barry in Phil. Trans., 1841, in recognition of the persistence of nuclei in the textures after development has ceased.

[6] Zeit. für Wissen Zool., bd. iii. p. 348.

[7] Würzburg Verhandl., bd. ii., 1851.

[8] Virchow's Archiv, 1855.

regarded as a most important contribution to our anatomical and physiological knowledge. For the connective tissue, beyond all others, is most extensively distributed throughout the body, so that an ever present cell and nuclear containing texture is by it provided. Not only does it, in its various modifications, constitute many special structures, as tendons, ligaments, fasciæ, the cornea, vitreous body, Whartonian jelly of the umbilical cord, etc., but it enters into the formation of the skin, mucous, serous, and synovial membranes, of muscles, blood and lymph vessels, of nerve-centres, and of nerves. It is found also in the glands in considerable quantity, varying, however, in amount in different instances, and serves as a sort of framework in which the vessels and tubes or follicles with their epithelial contents are embedded. That it is present in the majority of the parts I have enumerated, all anatomists will, I suppose, admit; but there are not wanting pathologists who deny its existence in some of them, and employ this as an argument against the general applicability of the doctrine of continuous cell-development. Of these parts, therefore, it will be advisable to speak with more precision. Thus it has been stated that no structure containing corpuscles exists in the white substance of the brain, and that the cells of pus, cancer, and tubercle, sometimes found in it, could not, therefore, arise from any such source.[1] But that cell-forms do lie amidst the nerve-fibres of the white substance has been satisfactorily established by the researches of Virchow, who has pointed out a very delicate connective tissue containing cells and nuclei, termed by him Neuroglia,[2] between the fibres and bloodvessels of the white substance, not only in the brain, but in the olfactory and auditory nerves; and I have placed under the microscope, in the adjoining room, several preparations in which the presence of numerous distinct corpuscles between the fibres of the white substance of the healthy human brain may be clearly seen.[3]

[1] Dr Bennett, in his Lectures on Clinical Medicine, pp. 153, 216, 3d edition, 1859.

[2] Cellular Pathologie, Lecture 13.

[3] These preparations were made by Mr Stirling, the assistant-conservator to the Anatomical Museum of the University, who has shown great skill in carrying out various methods of displaying the structure of the nervous system. They consisted of a section through the corpus callosum, a section through the white medullary centre of a cerebral convolution, and a section through the white substance of the cerebellum. They were obtained from a healthy human brain hardened in spirit, then steeping the sections for about ten minutes in solution of chromic acid, and afterwards tinting with carmine. By this process the corpuscles, tinted red, could be most accurately examined; and, without entering at this time into any detailed description of their arrangement, it may be sufficient to say that they were well-defined oval or circular corpuscles, in many of which nuclei could be seen, that they were seated between the nerve-fibres, and that they could not be confounded with the nuclei of the coats of the bloodvessels, for, as could be readily and precisely ascertained, they were altogether distinct from them. Lockhart Clarke, also, as quoted below, p. 442, has described nuclei abundantly scattered throughout both the white and grey substance of the cerebrum and cerebellum.

By the observations of Lockhart Clarke[1] and others,[2] a delicate connective tissue, containing multitudes of minute cells and nuclei, has been demonstrated between the fibres and bloodvessels of the columns of the cord, and the presence of connective tissue between the fibres of the ordinary distributory nerves is a matter of everyday observation.

In the kidney, also, some have denied the existence of any connective matrix substance between the tubes and vessels of the cortical part, and the accuracy of the observations originally made by Mr Goodsir[3] has been disputed. But the investigations of Dr Johnson,[4] and, still more recently, the exhaustive treatise of Arnold Beer,[5] have satisfactorily proved the correctness of his statements. The last-named observer has also described and figured the cell-elements of this connective matrix substance.

In the liver the connective tissue may be traced readily enough along the vascular trunks, forming the well-known Glisson's capsule; and in some animals, as the pig, polar bear, and camel,[6] it may be seen distinctly to separate the ultimate lobules of the gland from each other.

The brief review now given will, I think, be sufficient to show that cellular or nuclear bodies exist both in the proper structures of the organs and in the matrix of connective tissue which binds them together. This universal diffusion throughout the textures of bodies possessing definite organic forms is in itself a powerful argument in favour of the supposition that they possess definite properties.[7] The existence of these structures during the periods of development and growth, their persistence after these processes are completed, and the changes which take place in them during disease, all speak strongly of their physiological and pathological importance.

And now we may proceed to the examination of some of the leading pathological changes which take place in the elements of the textures. And, FIRST of all, we will speak of those which occur in inflammation, and which lead to the formation of the so-called exudation-corpuscles and of pus.

1*st, In the Connective Tissue.*—This, above all others, is the

[1] Philosophical Transactions, p. 441, pl. xxii. fig. 48, 1859.

[2] F. Goll. Denk. der Mediz-Chir. gesell. d. Kanton Zurich, 1860. J. Dean, Micros. Anat. of Lumbar Enlargement of Spinal Cord, 1861.

[3] London and Edin. Monthly Journal of Medical Science, May 1842.

[4] Article "Ren" in Todd's Cyclopædia. Mr Bowman also evidently recognised this substance, for he states that "the ducts and bloodvessels are seen to be embedded in a sort of matrix, apparently homogeneous, but probably having a cellular structure." Phil. Trans., 1842, pp. 70, 71. See, also, Kölliker's Handbuch.

[5] Die Bindesubstanz der Menschlichen Niere, Berlin, 1859.

[6] The distinct separation of the lobules of the liver of the camel from each other is beautifully shown in preparations in the comparative anatomy collection in the University of Edinburgh Anatomical Museum.

[7] Goodsir, Anat. and Path. Obs., pp. 1, 24. Paget, Lectures, p. 57, 1st ed. Savory, Phil. Trans., 1855, p. 254.

tissue in which the process of suppuration occurs most frequently and readily, which is in part accounted for by its extensive distribution and in part by its structure. For, in the latter respect, it approaches most nearly to embryonic tissue, *i.e.*, to tissue in which metamorphosis is most readily induced.

From recent investigations into the effects of irritants upon, and the process of suppuration in the loose areolar or subcutaneous connective tissue, it has been seen that although an exudation may, and certainly does, not unfrequently take place in it, yet that the changes which result in the formation of pus are set up, not in that exudation, but in the corpuscles of the connective tissue.[1] Their nuclei at first present distinct indications of being about to divide, for constrictions form at intervals in their sides, and as the process advances a complete separation is effected. This division may be multiplied to such an extent as to fill the corpuscles with many nuclei, which gradually assume the characters of pus-cells, and form small microscopic points of pus. Through persistence and extension of the process, the various corpuscles in the affected area undergo this change; their cell-walls and the intercellular substance disappear, the numerous minute spots of pus run together, and an abscess of a size proportioned to the extent of the irritated area is produced. In the more compact forms of connective tissue, as in tendons and periosteum, phenomena of a similar nature have been traced.[2]

In the cornea, which is now regarded as a modified form of connective tissue, the changes induced by irritation and inflammation have been most carefully studied, and the opacity which arises has been seen to commence in the connective-tissue corpuscles.[3] Dr His, who has especially studied the process of inflammation in this structure, has distinctly pointed out that the changes which occur depend upon increase in size of the cornea-cells and division of their nuclei, which division in some cases proceeded to such an extent, that twenty or more nuclei existed in a single mother-cell. By a further continuance of the process, these nuclei gradually assumed the appearance of pus-corpuscles.

2*d*, *In Cartilage.*—In cartilage, a texture in which, as in the cornea, we are enabled, through the absence of bloodvessels, to eliminate all effects which, in the so-called vascular textures, might be supposed to be produced by the occurrence of an exudation, the well-known researches of Professor Goodsir,[4] amplified and extended by Dr Redfern,[5] have proved most conclusively that the inflamma-

[1] Virchow, Lecture 19; Förster, Atlas, taf. xxxi. fig. 3; Billroth, Beiträge, pp. 26 and 37; C. O. Weber, Virchow's Archiv, vol. xv.

[2] Billroth, op. cit., taf. ii. fig. 11; C. O. Weber, op. cit., taf. viii. fig. 1.

[3] Virchow in his Archiv, b. iv.; Strube, Der normale Bau der Cornea, 1851; His, Beiträge sur norm. and path. Hist. der Cornea, Basel, 1856; Rindfleisch, Virchow's Archiv, 17th vol. p. 239, 1859; C. O. Weber, op. cit., p. 11; Förster, Atlas der Pathologischen Anatomie, 1859, taf. xxxiii. fig. 3.

[4] Anat. and Path. Observ., p. 17.

[5] Abnormal Nutrition in Articular Cartilages, 1850.

tory and ulcerative processes in it are due to the formation of masses of nucleated cells within the cartilage corpuscles. By the persistence of this proliferating process, alteration and destruction of the wall of the cartilage corpuscle and the intercellular substance is occasioned. Dr Redfern, however, expressed doubts, whether from these proliferating cartilage cells, pus corpuscles could be formed. But more recent researches[1] would appear to have demonstrated that, in purulent inflammations of joints, the pus-corpuscles may take their rise not only through changes in the synovial membrane, but through endogenous multiplication in the cartilage-cells themselves.

3*d*, *In Bone.*—If a bone, in which the processes of ulceration and suppuration are going on, be microscopically examined, it may be seen that, in addition to the softening due to the removal of the earthy matter, other textural changes have set in. The Haversian canals have become dilated by the absorption and removal of their osseous walls, so that adjacent canals are thrown together and spaces and cavities are produced in the texture. At the same time these cavities become filled with a cellular growth—the granulation substance—from the free surface of which pus-corpuscles are thrown off;[2] the immediate cause of the removal and absorption of the bone, and the formation of the spaces and cavities being the development of the cellular growth. But these changes are not confined to the production of a cellular mass in the Haversian canals; for alterations may be observed in the lacunæ and canaliculi of the intermediate osseous texture. Minute drops of fat in the first instance appear in them, and, as this form of degeneration increases, the lacunæ and canaliculi, owing to the softening and absorption of the intervening substance, gradually widen out, until at length several adjacent spaces are thrown together. In this manner, that perforated worm-eaten appearance is produced which is so characteristic of a carious bone.[3] But along with this destruction of the osseous substance, a growth of cells in the enlarged spaces now occurs. These cells would appear to arise in one or other of two ways, either by the multiplication of the original nuclei of the bone lacunæ,[4] or by the extension into the spaces of granulation-cells with accompanying bloodvessels, either from the periosteum, medullary membrane, or Haversian canals.[5] From these granulation-cells pus-cells may proceed in the usual manner.

4*th*, *In Muscles.*—In inquiring into the effects of irritants upon, and the mode of formation of pus in muscles, we shall experience perhaps somewhat greater difficulties in deciding upon the source

[1] C. O. Weber, Virchow's Archiv, vol. xiii. p. 79; Förster, Atlas, pl. xxxiii. fig. 1, p. 65; Barwell, on Diseases of the Joints, 1861.

[2] Goodsir, op. cit., pp. 15, 71.

[3] Von Bibra, Annalen der Chemie und Pharm., vol. lvii. p. 356, 1846; C. O. Weber, Virchow's Archiv, vol. xv.

[4] Virchow, Lecture 18; Förster, Atlas, taf. xxxi. fig. 6, taf. xxxiv. fig. 4 Barwell, p. 238.

[5] Billroth, Beiträge, p. 51; C. O. Weber, op. cit.

from whence the pus-corpuscles arise than in the textures previously considered. For a muscle is in its structure a complex organ, one which consists not merely of the proper contractile muscular fibres, but of a considerable quantity of connective tissue, which subdivides the muscle into its constituent bundles, and also lies between the fibres of which the bundles are composed. Irritating agents applied to a muscle, act not only on this intervening connective tissue, but on the muscular fibres themselves.

For whilst fully recognising the great influence exercised by the connective tissue or its allies, bone, cartilage, and epithelium, in the various pathological changes which may take place, not only in the parts composed exclusively of these textures, but in those in which they may be intermingled with other tissues, yet I am not disposed to limit the production of these changes so exclusively to the connective substances as Virchow would appear to do, or to exclude the cells and nuclei of the other textures from all participation in the production of morbid structures. And in the case of muscles, the proper nuclei of the fibres undoubtedly play a most important part, not merely in the formation of pus, but, as I shall afterwards point out, in the development and propagation of cancer in their substance.

When inflammation takes place in a muscle, in addition to the long-recognised destruction of the muscular substance occasioned by fatty degeneration of many of the fibres, productive changes may be traced in the nuclei of others of the fibres and in the corpuscles of the interposed connective tissue.[1] These appear to arise in the first place in this connective tissue, in which the phenomena of nuclear division and endogenous cell-multiplication, occasioning the production of large mother-cells, occur in a manner closely corresponding to that which has already been described in the areolar and tendinous tissues. By these processes cell-forms are generated completely identical in appearance with those of pus. The multiplication of these cells in the connective tissue not unfrequently goes on to such an extent as greatly to interfere with the examination of the fibres themselves. But in favourable specimens a distinct nuclear multiplication may be seen to have occurred within the fibres. And this process may be traced in different specimens, from the simple separation of a nucleus into two, to the much more advanced stage in which, through the persistence of

[1] Virchow, Archiv, iv. p. 313; viii. p. 32; Cellular Pathologie. Förster, Handbuch, p. 383; Atlas, taf. xxxi. fig. 5. Böttcher, Virchow's Archiv, xiii. p. 227. Billroth, op. cit. C. O. Weber, op. cit. Sczelkow, Virchow's Archiv, xix. p. 215, 1860.—Of the above authorities, Weber has most completely worked out these suppurative changes in the muscle; see his plates viii. and ix. Both Böttcher and Weber have described and figured the nuclei both of the muscular fibre and the sarcolemma as contained in distinct cells, which they consider to belong to the system of connective-tissue corpuscles. But, as has been well said by Dr Haldane (Edin. Med. Jour. Nov. 1862, p. 443), whether we adopt this view, or look upon them as nuclei proper to the fibre, the further process of development of the new cells from them is the same.

this nuclear division, long rows or crowds of corpuscles are formed, which gradually assume the form and general appearance of pus-corpuscles. By the continuance of this process, destruction of the fibre occurs; it assumes a very jagged and irregular outline, and ultimately altogether disappears.

And here I would especially point out the important evidence which these observations on the origin of pus-cells within the muscular fibre affords of the correctness of the doctrine, that they take their rise from pre-existing textural elements, and not in a structureless or granular exudation. Even the most strenuous advocates for the exudation hypothesis are constrained to admit that the increase of cell-forms in inflammations of cartilage and the cornea is due to germinative changes in the proper cell-elements of those textures. And this they endeavour to explain by stating that these tissues are altogether extra-vascular, and consequently beyond the reach of any exudative infiltration, whilst the muscular, glandular, and other tissues are more or less abundantly supplied with vessels. But though bloodvessels exist in the substance of the muscles, and that too in large numbers, yet the individual fibres—nay, the minutest corpuscles of the interfibrous connective tissue—are in their kind, though not, of course, to the same degree, as extra-vascular as cartilage or the cornea. Are we then to suppose that an exudation poured out from the adjacent vessels passes through the sarcolemma into the substance of the fibre, and that from this the pus-corpuscles found within it take their rise? Such a supposition is in the highest degree improbable; for a muscular fibre is a compact solid structure. It is composed of contractile sarcous particles, with intervening scattered nuclei, which are included within a membranous sarcolemma, and so closely packed together that no space or vacuity in which an exudation could find room exists. The same mode of argument may be applied also in explanation of the formation of pus-corpuscles within the proper elements of others of the textures, as the lacunæ of bone, epithelium, etc., all of which are distinctly extra-vascular. And thus, without doing more than merely allude to the absence of anything like satisfactory proof of the spontaneous origin of pus-corpuscles in an exudation, it is possible, by employing the principle of exclusion, to show the complete insufficiency of such an hypothesis to account for their mode of origin.

5th, In Nerves.—The production of pus in nerves so closely corresponds to that which I have just described in muscles, that it is needless to enter into details. It may suffice to say, that it may proceed both from the corpuscles of the connective tissue lying between the fibres, either by a multiplication of their nuclei or by an actual division of the cells themselves, and from the proper nuclei of the neurilemma of the fibre.[1]

[1] Billroth, op. cit., p. 47. C. O. Weber, op. cit., p. 24. Hjelt, Virchow's Archiv, xix. p. 364, 1860.

I may however, perhaps, more particularly refer to an observation of Professor Förster on the origin of the so-called exudation-corpuscles in the white substance of the brain, in a case of encephalitis.[1] New-formed cells existed in such numbers as to obscure more or less completely the nerve-fibres. In some the nucleus was single, but in others two and three were present. In other cases the cells themselves were observed to be constricted in the middle between the two nuclei as if in the act of dividing. When the circumference of the new-formed inflammatory mass was examined, the pre-existing cells of the connective-tissue matrix of the white cerebral substance were seen to be undergoing an abundant increase by division. Through this process the new-formed cells had evidently been produced.

6*th*, *In Mucous Membranes.*—When a mucous membrane inflames, not only is there a discharge, generally profuse, of more or less modified mucus from its surface, but at the same time a rapid production of inflammation-corpuscles occurs, and a great tendency to the formation of pus exists. Whence, then, do these corpuscles arise? To enter properly into the consideration of this question, it will be necessary that we should briefly direct our attention to the anatomy of the membrane itself. The general conception entertained of its structure is that it consists of three parts: 1*st*, An extremely thin, transparent, and homogeneous membrane, perfectly continuous, and without any aperture or appearance of structure. This membrane was particularly described by Mr Bowman, and named by him "basement membrane." 2*d*, An epithelium, varying in its shape and thickness in different localities, and consisting of one or several layers of cells situated on the superficial or free surface of the basement membrane. 3*d*, Areolar connective tissue intimately related to the deeper or attached surface of the basement membrane, and therefore completely separated by it from the epithelium on the free surface. In this connective tissue the nerves, blood and lymph vessels lie. This general conception of the structure has been extended not only to the various ducts, glands, and fossæ, which open on the free surface of any mucous membrane, but to the serous and synovial membranes and the skin; although it is admitted that, whilst the epithelial and connective tissue elements are always capable of demonstration, yet, that the basement membrane is not at all times to be isolated. But numerous careful investigations made of late years into the structure of the mucous and other membranes and the skin have led many anatomists to doubt the existence of any such entire, continuous, homogeneous membrane between and separating the epithelial and connective-tissue elements as Mr Bowman described, and thus it is now believed that no sharp line of demarcation between these textures exists. They gradually pass into

[1] Atlas, p. 63, taf. xxxii. fig. 3.

each other, and in some localities, indeed, the cell-elements of the one are anatomically continuous with those of the other. It would be possible, did time permit, to adduce many observations in support of this statement, but it may suffice, perhaps, to refer only to those made on the urinary, tracheal, intestinal, and buccal mucous membranes.

The structure of the mucous membrane of the bladder, ureters and pelvis of the kidney, has been most carefully described in an essay by Burckhardt.[1] He has pointed out that beneath the flattened scale-like epithelium which forms the free surface of the membrane there exists a second layer of cells, some of which are rounded or oval, others caudate; and these latter are so arranged as to lie with their long axes perpendicular to the surface of the membrane. Many of these cells are much elongated, and possess remarkable modifications of shape.[2] In the intervals between their narrow tail-like processes, the oval and rounded cells lie. The cells of this second layer rest directly upon and not unfrequently their caudate ends pass somewhat into a third layer, called by Burckhardt the matrix. This matrix consists of numerous rounded or oval cells, slightly separated from each other by short and delicate fibres. By its deeper aspect it gradually passes into connective tissue, possessing the usual characters. The bloodvessels pass through the connective tissue into the matrix, and form a capillary network immediately beneath the epithelial cells of the second layer.

In the tracheal mucous membrane, after many observations, the same anatomist satisfied himself that no structureless basement membrane existed between the epithelium and subjacent connective tissue.

[1] Virchow's Archiv, 17th vol. p. 94, 1859.

[2] Some time ago, Dr W. T. Gairdner requested me to examine a urinary sediment obtained from a man, at that time a patient in one of his wards in the Royal Infirmary. I found in it various cell-forms, as mucus-corpuscles, and cylindrical and squamous epithelium-cells. But, besides these, there were other forms, such as are represented in the lower of the two rows in the accompanying fig. 1. Those to the left were probably cells of the second layer

Fig. 1.

described in the text. But, in addition, several examples of the curiously elongated and variously twisted cells, such as are represented to the right of the same row, were observed. Burckhardt has also figured, from a drawing of Professor Beckmann, cells of a somewhat similar character which were observed in the examination of the mucous membrane of the ureter.

In the mucous membrane of the small intestine a very remarkable arrangement connected with the epithelial cells of the intestinal villi has been recently described, which would appear to establish a direct anatomical continuity between them and the corpuscles of the sub-epithelial connective tissue of the villus.[1] Long processes have been seen passing off from the narrow deeper ends of the epithelium-cells, which enter the substance of the villus, and become continuous with the corpuscles of the sub-epithelial connective tissue. The presence of such connecting structures of course does away altogether with the existence of a continuous basement membrane in this locality. In the buccal mucous membrane, also, long processes have been traced by Billroth[2] from the epithelial cells into the sub-epithelial connective tissue of the papillæ of the tongue. It will now, therefore, be more correct to consider a mucous membrane as consisting of one or more layers of epithelial cells resting on a bed of connective tissue.

Various observers have now demonstrated that, when a mucous membrane inflames, the corpuscles of pus may take their rise either in the interior of the epithelial cells themselves or in the corpuscles of the subjacent connective tissue.[3] Thus they have been seen within the enlarged epithelium-cells of a hepatised lung,[4] in the epithelial cells of the bladder and ureter,[5] in the epithelium of the bile-duct in a case of pyle-phlebitis,[6] in the squamous epithelium of the conjunctiva and the ciliated epithelium of the bronchial tubes,[7] and, as Dr Haldane has recently described,[8] in the epithelial cells of the trachea and bronchi in variolous inflammation of those tubes.

But though pus may form in the interior of the epithelial cells, yet it is probable that the chief seat of its production is in the corpuscles of the sub-epithelial connective tissue; and of its origin in this tissue several observations may be adduced. Thus Burckhardt (op. cit.) has described pus-cells as arising from division of the

[1] Heidenhain in Moleschott's Untersuchungen, vol. iv. p. 251, 1858.

[2] Müller's Archiv, 1858, p. 159. The following additional examples of the connexion between epithelial and sub-epithelial structures have been observed. Luschka (Virchow's Archiv, ix. p. 567) has seen the epithelial cells of the endocardium connected by long processes with the connective-tissue corpuscles. Stilling, Bidder, Kupfer, and Luschka (quoted by C. O. Weber) have traced connexions between the epithelial cells lining the central canal of the cord and the cells of the grey substance. Lockhart Clarke has also described connexions between the epithelial cells of the central canal and the small cells or nuclei immediately outside them. Phil. Trans., 1859, p. 456.

[3] Virchow, Cell. Path., Lecture 19.

[4] Buhl, Virchow's Archiv, vol. xvi. p. 168, 1859.

[5] Remak, ibid., vol. xx. p. 198. Both Remak and Eberth (ibid., vol. xxi. p. 106) have observed appearances which seemed to show that mucus-corpuscles also may form in the interior of the epithelium-cells of the mucous membrane.

[6] Buhl, ibid., vol. xxi. p. 480.

[7] Rindfleisch, ibid., vol. xxi. p. 486.

[8] Edinburgh Medical Journal, November 1862, p. 438.

nuclei of the cells of the sub-epithelial matrix layer of the urinary mucous membrane. Rindfleisch (op. cit.) has seen the same changes taking place in the connective tissue of the conjunctival and bronchial mucous membranes; and in these cases, as in the formation of pus in the ordinary areolar connective tissue, with the increase of the pus-cells the fibrous element of the connective tissue gradually disappears.

An examination which I made a few weeks ago of the inflamed mucous membrane of the pelvis of a kidney and ureter illustrated in a very striking manner some of the phenomena connected with the formation of pus in the sub-epithelial connective tissue.[1] The free surface of the membrane was covered with a layer of granular and molecular matter, beneath which, and extending for some distance into the substance of the swollen and thickened membrane, were multitudes of small closely-crowded cells, like pus or the so-called exudation corpuscles. They were so numerous that the natural texture was completely hidden by them. Still deeper the cells diminished in numbers, and arranged themselves in groups, which evidently corresponded to the sites of the original corpuscles of the connective tissue, and between these groups of cells portions of the fibrous elements of the texture might be seen. But in all these deeper parts of the tissue, where the cell-forms were present, and evidently, from their general aspect, most capable of undergoing development and increase, the amount of granular and visible molecular matter, both free and within the cells, was comparatively small. Now, if the hypothesis of the formation of pus or exudation corpuscles by the aggregation of granules or visible molecules were correct, we should naturally expect to have found, in those parts of the inflamed membrane in which the process of cell-formation was to all appearance most actively going on, the molecular and granular matter in considerable quantity. But, on the contrary, it was at a minimum in these localities, and was present in greatest amount on and next the free surface of the membrane, *i.e.*, at the part where, from various causes, as contact with the urine and greater separation from the sources of nutritive supply, disintegration of texture would most naturally take place. Hence I cannot but conclude that the granules and visible molecules found in such cases are products of textural disintegration, and not agents in its formation.

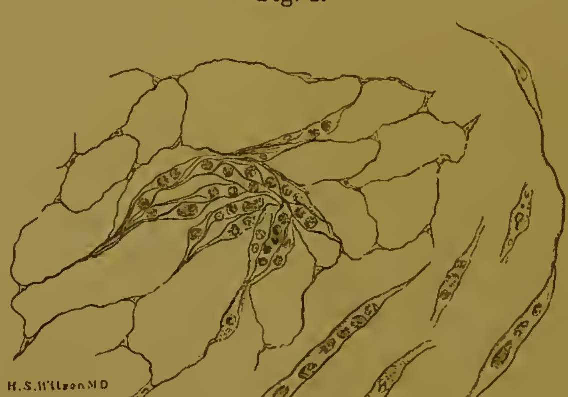
7*th*, *In Serous Membranes.*—In the serous as in the mucous membranes satisfactory evidence has been adduced to show the production of pus both from the epithelial cells and sub-epithelial connective tissue of which these membranes are composed, although it is probable that in them the endogenous formation of

[1] Both in this and the serous membrane described further on, the examination was conducted on thin sections made at right angles to the surfac with a Valentin's knife. The sections were treated with glycerine and acetic acid. By this method all the structures may be examined *in situ*, and with no disturbance of their natural relations.

pus in the epithelium-cells takes place to a much smaller extent, and is less enduring than in the connective tissue. The investigations of Rindfleisch[1] would indeed appear to prove that when a serous membrane inflames, along with the exudation of a coagulable material from the blood, the epithelium loosens and falls into its constituent cells, the nuclei of which may undergo increase and development, and the epithelium cells themselves even may assume the appcarance of pus-corpuscles. But it is more probable, as Cohnheim's observations indicate,[2] that the cells after being detached, being cut off from their nutriment, undergo fatty and granular degeneration, so that their cell-membrane disappears, and their complete destruction takes place.

After the epithelium has becn detached, the formation of pus goes on in the corpuseles of the sub-epithelial eonncetive tissue. And I may, in support of this statement, describe the appearanees which I have seen in the course of the examination of an inflamed pleura, which I made early in the month of January of the present year. The free surfaee of the membrane was covered by a thin layer of soft yellow inflammatory lymph, beneath which the membrane was swollen and very vascular. The lymph itself consisted of small, pale, faintly granular cells, having the well-known appearance of the so-called exudation-corpusclcs. They were compactly arranged, so that the quantity of intercellular substanee was but small. The epithelium had altogether disappeared. The sub-epithelial connec-

Fig. 2.[3]



tive-tissue eorpuseles were swollen, and, instead of possessing a single nucleus, contained in some eases two, in others a larger number, even up to half-a-dozen, of distinct, pale, in many cases eircular, bodies, elosely eorresponding in form and appearance to the corpuseles of the inflammatory lymph with whieh the surfaee

[1] Virchow's Archiv, vol. xxiii. p. 519, 1862.

[2] Ibid., vol. xxii. p. 516.

[3] Fig. 2.—Corpuscles of the sub-epithelial connective tissue of the inflamed plcura described in the text.

of the membrane was covered. These were, without doubt, derived by division from the original nucleus of the connective-tissue cells. This process of endogenous multiplication was seen to the greatest advantage in those parts of the connective tissue in which the proliferation was in its early stage, for here individual as well as small groups of corpuscles could be separately examined; but in those portions of the membrane in which the production of new cells had been for some time going on, the new structures were so numerous as entirely to obscure the original elements of the texture. Changes of an exactly corresponding nature have been traced by Cohnheim (op. cit.), and with much more detailed minuteness, in inflammations both of the pericardial and peritoneal membranes.

8*th*, *In the Skin.*—In the skin, as in the mucous and serous membranes, both epithelial cells and a sub-epithelial connective tissue are met with: the former constituting the cuticle or epidermis, the latter the cutis or true skin. Both the cuticle and cutis participate in the process of suppuration.[1] The corpuscles of the connective tissue, of which the cutis is composed, go through all those productive changes of nuclear division and mother-cell formation which I have already described as occurring in the formation of pus in the connective tissue in other parts. The cuticle or epidermis possesses considerable relative thickness, and consists of many layers of cells, which may be regarded as arranged in two strata—a superficial or horny stratum, and a deeper, softer stratum, known to the older anatomists as the rete Malpighii. The more superficial of these two strata does not appear to take any part in the suppurative process, but either becomes elevated, as in the formation of blisters, or else separates in fine scales, as in the course of pointing of an ordinary abscess. The cells of the rete Malpighii are those in which the pus is produced. They pass through all those changes of constriction and division of the nucleus which result in the formation of groups of nuclei in a single cell, and various forms of division of the cell may not unfrequently be seen. From these, as from the instances already cited, pus corpuscles are produced in a quantity proportioned to the intensity of the process and the extent of the area affected. At the same time, as so frequently happens, not only in inflammation of the skin but of other textures, many of the cells undergo destruction by fatty degeneration.

9*th*, *In Secreting Glands.*—If we were now to direct our attention to the secreting glands, and inquire into the changes which take place in them in the course of the inflammatory process, we should find that both the secreting epithelium-cells and the connective-tissue matrix take part in the process. In illustration, perhaps, it may suffice if we limit ourselves to an examination of one of these glands, and we will take, as an example of the rest, the kidney. It has long been known that the secreting epithelium of the kidney-tubes is materially affected in inflammation of the gland, and the various

[1] Virchow, Lecture 19; Billroth, Beiträge, p. 41; Weber, op. cit.

changes which it undergoes have been so often described that it is needless for me to enter into them; but the part which the eonnective-tissue matrix plays in the process has been comparatively little studied. The treatise of Arnold Beer, already cited, will, however, supply us with some excellent illustrations of the changes which occur in it. In some forms, and at certain stages, of inflammation of the cortieal substanee of the kidney, he has observed the interstices between the urinary tubes, normally oecupied by the connective-tissue matrix, greatly inereased in size and eontaining a number of small, pale, circular corpuscles, corresponding in appearanee to the lymph or white blood-corpuscles; but whieh, as he fully satisfied himself, were in no way derived from the bloodvessels. Where these changes were only commencing, the influence exercised by the corpuseles of the eonnective tissue in the produetion of these new cell-forms might be traced. They were much enlarged, their processes broader and more distinct, their star-like shape in consequence much more strongly pronounced, and in them several round nuelei were to be seen, indicative of the commeneement of an endogenous development.[1]

In other cases he has seen in the enlarged intertubular interstices small round eells, having all the character of pus corpuscles (p. 176). In these places, also, the conneetive-tissue corpuscles were much inereased in size, and presented many of the characters of branched ganglion cells; and in these star-like or spindle-shaped structures numerous nuelei were contained. Many other changes have also been traced in the intertubular eonnective substance, such as the occurrenee of fatty degeneration, the spindle-like eells of the conneetive tissue at first presenting fat-granules in their interior; but as the proeess continues, all traces of these corpuscles disappear, and the fatty partieles are erowded together or scattered about irregularly in the intercellular substance (p. 87). In the same connective-tissue matrix oceur those ehanges which result in the production of the various forms of contracted kidney.

The rapid glance which we have now cast over the productive changes whieh occur in the textures when the inflammatory process is set up, will, however, I think, be sufficient to show that the formation of the so-called exudation-corpuscles, as well as those of pus, depends upon changes in the textural elements of the parts themselves, and not in the exudation poured out amongst them. But this influenee of the textural elements is not limited to the later stages of inflammation, and observations are not wanting to prove that in the early stages also they play a most important part. On this point, however, I must content myself with simply referring to the many excellent observations of Professor Lister,[2] which, from the methodical manner in which they were conducted, from the care which has

[1] Beer describes these ehanges as constituting an interstitial eellular hyperplasia, p. 56, *e. s.*

[2] Philosophieal Transactions, 1858.

evidently been taken to eliminate errors, not only in the observations themselves, but in the conclusions which have been drawn from them, must be regarded as most satisfactory contributions to our knowledge.

II. CANCER.—When a cancer is examined microscopically, it is seen to consist essentially of cells and nuclei, embedded in an interstitial substance or stroma. The cells and nuclei constitute the well-known cancer-cells and nuclei, and present forms and appearances which may be regarded as characteristic of the disease. They are evidently new formations. The stroma, again, may consist either of the remains of the original texture of the part, as is mostly the case in scirrhus, or it may be, like the cancer-cells between which it is situated, a new formation also. In what manner, and from what source, do these new-formed structures arise? To these questions I think I shall be able satisfactorily to reply, that they arise from changes in the textural elements—the pre-existing cells and nuclei—of the part, and do not spring up spontaneously by any process of precipitation or aggregation of granules in a structureless or granular exudation.

In the development of these new-formed cancer-cells, the corpuscles of the connective tissue play an important, though not an exclusive, part; for I think that I shall be able to advance sufficient evidence that the cells and nuclei of others of the textures participate in the process, and this not only in one, but in others of the leading varieties of cancer.

There is, indeed, no organ in the body in which the productive changes leading to the development, growth, and extension of cancer can be more exactly studied than the muscles. For the textures of which they are composed can be readily and conveniently prepared for microscopic examination, the margins of the muscular fibres can be precisely defined, and the alterations of structure occurring in them can be noted without much difficulty. In the scapular muscles of the man whose case Mr Syme has related to us this evening I had such excellent opportunities of tracing many of the phenomena attendant on the development and growth of soft cancer in the muscles, that I could not advance a better illustration of the process.[1] The cancer had evidently commenced at the glenoid fossa of the scapula, and had extended from this part backwards on both the dorsal and ventral surfaces of the bone, so as to form a large and well-marked tumour. By its progress, not only was the glenoid fossa and the neck of the scapula softened and destroyed, but the muscular structures on the dorsal and ventral aspects were involved in, and changed by, the disease. It is of the alterations which they displayed that I shall especially speak. The

[1] Before the delivery of this Lecture Mr Syme related the case of and exhibited a patient, from whom he had excised the whole of the scapula, leaving, however, the arm, for cancerous disease of the scapula and its muscles. See on p. 951.

fibres of the proper muscles of the scapula had to a great extent lost their normal ruddy tint. Those situated over that part of the bone with which the tumour was in connexion were displaced from their position, thickened, and incorporated with the exterior of the tumour, for which they formed a sort of capsule. But this loss of colour was not confined to those parts of the muscles actually in contact with the tumour; it was seen also in the fibres beyond, which were pale, dull yellow, or buff-coloured.

When examined microscopically, very important structural changes were seen to have taken place in their interior. In many of the fibres fatty degeneration might be traced in its various gradations, from that first stage where the distinctness of the transverse striation was scarcely affected, and where but a few fatty granules existed, to that later stage where the fibres were so completely filled with highly refracting granules, that all trace of the proper muscular substance was completely destroyed. But in others of the fibres changes of another character could be traced, especially after the addition of acetic acid. These were produced by a multiplication more or less marked in different cases of the nuclei of the fibre. In some fibres the nuclei formed long strings or chains,—those in the same row lying with their ends almost in contact, and closely following each other. The number of nuclei in a row varied considerably in different cases, from two to a dozen, or even more. Some of these strings were situated close to the edge of the fibre, and, therefore, must be regarded as a multiplication of the nuclei of the sarcolemma. Others, again, were in its substance, and produced by a proliferation of the nuclei proper to the fibre itself. In

Fig. 3.[1]

some of the fibres, the nuclei, instead of increasing in this linear manner, had multiplied in such a way as to form little clusters in the

[1] Muscular fibres from the exterior of the soft cancerous tumour, displaying different stages of proliferation of nuclei. *a*, Early stages. *b*, More advanced stage.

centre of the fibre; and in cases in which this increase had largely taken place, the whole diameter of the fibre at that spot was completely occupied by closely packed nuclei. In many specimens, both the linear and clustered arrangements could be seen in the same fibre, and when these were largely developed, all traces of transverse striæ had disappeared, and the fibres were completely filled with the young brood. A still further stage, viz., disintegration of the fibre, was observed in many of these; they had lost their regularity of outline, and deep indentations were present in their sides. They were evidently breaking up and adding their quota of proliferating contents to the collections of nuclei and small oval and rounded cells, which existed in large quantities in those localities in which these disintegrating fibres were seen.

These appearances seem to me to afford conclusive evidence that, when cancer affects the muscles, destruction of their fibres takes place, through proliferation of their own proper nuclei and those of the sarcolemma. And that as this destructive process extends, the cancer grows and involves more and more of the muscular substance. The increase in its size and the enlargement of its boundaries being evidently due to the multiplication of the nuclei, which, through the disintegration of the fibres, are continually being added to the circumference of the cancerous tumour, and there assume the appearance and characters of true cancerous elements.

In the instance I have now brought forward, it has been stated that two changes—the one fatty degeneration, the other nuclear proliferation—were taking place in the fibres of the muscles of the scapula. But the product, in the one case, was merely fat, which of itself possesses no further power of increase; whilst, in the other, nuclei were produced, which, by their subsequent development and growth, assisted materially in the extension of the disease.

The development and growth of cancer in muscles, through multiplication of their nuclear elements, is not, however, confined to soft cancer, but is shared also both by epithelial cancer and by scirrhus. In scirrhus, excellent illustrations have been figured by Professor Weber of Bonn, in the muscular fibres of the tongue,[1] and by Dr Neumann in the pectoralis major muscle, in a case of hard cancer of the breast;[2] but, as their observations in most particulars agree with those I have just related, it is needless for me to detail them.[3] In the muscles of the tongue and lips, Weber has also traced (pl. xi. figs. 1, 2, 3, 4, 5, 6, 7) the development of epithelial cancer, not

[1] Op. cit., pl. xi. fig. 10.

[2] Virchow's Archiv, vol. xx. p. 152, 1860.

[3] Dr Haldane has, in the Edinburgh Medical Journal, Nov. 1862, p. 439, recorded a case, apparently of soft cancer, in which such changes as I have described were taking place in the muscles. In the same paper, he gives an excellent account of the production of a new formation, which he considers to be syphilitic, in the muscular substance of the heart, by proliferation of the nuclei of its fibres.

only through proliferation of the nuclei of the muscular fibres, but of those of the connective-tissue corpuscles also. By which processes, through endogenous reproduction, large mother-cells possessing epithelial characters were formed.

Now, in all the cases I have adduced, the formation of the cancer structures might be traced from the first division of the nuclei of the fibre up to the completed stage of cancer-cell development. And that, too, in a texture which, from its structure, gave no room for the existence of any exudation in it, and in which, therefore, the new-formed structures must have arisen from changes in the pre-existing elements of the tissue. And, indeed, a careful perusal of the writings of one of the most active advocates of the hypothesis, that cancer-cells arise by an aggregation of granules in an exudation, has satisfied me that, as yet, no conclusive evidence has been advanced in its support.

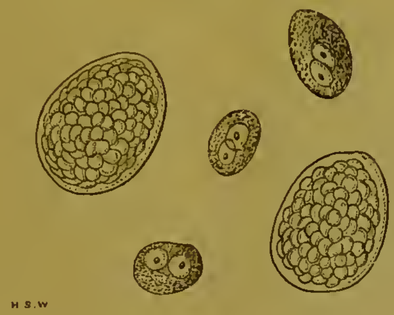
I have entered somewhat at length into the mode of development and growth of cancer in the muscular fibres, partly because it is in them that I have obtained the most satisfactory proofs of the nature of the process, and partly because from the construction of the fibre there is less possibility of committing errors of observation than in others of the textures; yet I do not wish it to be supposed it is in the muscles only that the textural changes, resulting in the production of cancerous growths, can be or have been followed. In the connective tissue Virchow first traced the development of cancer from pre-existing tissue elements, and he has figured and described the process from a case of carcinoma of the breast, in his nineteenth lecture. Professor Förster has also beautifully illustrated its production in this tissue in a case of carcinoma ventriculi (taf. xxvii. fig. 1). In this case, all the stages might be seen from the simple multiplication of the nuclei of the connective-tissue corpuscles to the more advanced condition in which the corpuscles were distended, with crowds of the new-formed cancer-cells.

These examples may be sufficient to show that pathologists are quite justified in ascribing the origin of cancer to changes in the pre-existing tissue elements. Their growth also in the locality which they primarily affect may, in a great measure, be accounted for by an extension of these textural changes beyond the spot in which they first began, so that not only the tissue first affected, but even those adjacent, may become involved in the disease. But we may consider that there is also proved for cancer a power of spontaneous growth, not only of the individual cells, but of the entire mass; and this latter by the endogenous multiplication of the nuclei and the formation of brood or mother cells. Examples of this mode of increase have been figured by Virchow,[1] Paget,[2] Bennett,[3] and Förster.[4] Some time ago, in examining portions of a soft cancer from the lower end of the femur, I saw many examples

[1] Archiv, iii. 197.
[2] Lectures, vol. ii. p. 439.
[3] Op. cit., p. 215.
[4] Atlas, taf. xxvii. fig. 2.

of these brood-cells, and in illustration of the process I append the following figure.

Fig. 4.



The extension of cancer in a part, through the textural changes just described, opens up a very interesting question, and one which ought not to be altogether passed over. In how far is the proliferation of nuclei in the tissues in the neighbourhood of a cancer to be taken as an index of the commencement of the disease in those tissues? Pathologists have long recognised[1] that cancer-cells not unfrequently are infiltrated amongst the tissues for some distance beyond the actual seat of the tumour itself, and that therefore the great rule followed by surgeons, of removing, not only the tumour, but a portion of the tissues surrounding it, is based upon a sound principle. Now, from what I have already stated, it would certainly appear that, in endeavouring to estimate the extent to which the surrounding textures are involved in the disease, it is not sufficient to take into consideration those parts merely in which well-marked cancer-cells are met with; but that any appearance indicative of multiplication of the nuclei of the pre-existing tissue elements, inasmuch as this is a stage initiatory to the development of cancer-cells, is to be regarded with suspicion, although this multiplication, inasmuch as it also precedes the formation of the corpuscles both of pus and tubercle, cannot be looked upon as conclusive.

III. Tubercle.—The peculiar material known as tubercle possesses, for the most part, one or other of two chief forms, which are distinguished as the miliary or granular and the cheesy tubercle; and between these many intermediate varieties may occur. Of these two leading forms the miliary is the most typical. When examined microscopically, it is seen to consist of small, pale, nucleated cells, some of which possess a single, others several nuclei. The cheesy tubercle, again, not only contains such cell-forms as are met with in the miliary, but many others, which, from their shrivelled, shrunken aspect, or from the fatty granules contained in their interior, indicate the commencement of degenerative changes. Mingled with these cell-forms are numerous granules and molecules, either fatty, calcareous, or pigmentary, with cholestearine

[1] See Bennett on Cancerous and Cancroid Growths, p. 104. 1849.

crystals and fragments of tissue, evidently the products either of degenerative changes in the tubercle-cells themselves, or in inflammatory material in the adjacent parts, or derived from disintegration of the texture in which the tubercle is situated.

How then do these tubercle-cells arise? The doctrine entertained up to a very recent period, and still taught by many pathologists, is that they arise in an exudation or deposit from the blood poured out into the tissue or organ in which the tubercular matter occurs. But evidence has been advanced to show that the tubercle-corpuscles, like those of pus and cancer, may and do take their origin in changes in the textural elements of the parts themselves. For proofs of this, as of so many of the other matters discussed in this Lecture, as well as for the first conception of this mode of origin of tubercle, we are indebted to Professor Virchow. He has pointed out that the connective tissue is the source from which these tubercle-cells proceed, and that their formation is always preceded and accompanied by changes in its corpuscles (Cel. Path., Lecture 20), which are closely comparable with those already described in the formation of the inflammatory exudation-corpuscles and of pus. By the persistence of this process in a part, a small cellular knot or tubercle, the miliary tubercle, is produced. Förster has also traced and illustrated in his Atlas (taf. xxxvi. fig. 1) the development of tubercle from the connective-tissue corpuscles in a case of pulmonary tuberculosis.

But when these tubercle-cells are once formed, they do not appear to possess as a rule much power of spontaneous growth, or even of maintaining themselves for any length of time, and in this respect they present an important difference to cancer, the cells of which not only grow and maintain themselves, but even multiply through endogenous development.[1] The cells of tubercle exhibit decided tendencies to shrivel, or wither, or to undergo fatty or other degeneration, and produce either cheesy tubercle, or some of the intermediate varieties between that and the miliary.

The epithelium-cells, also, in certain localities, would appear to assist in the production of tubercle by the formation in their interior of a brood of young corpuscles. But on this point I must satisfy myself with referring to the observations of Virchow and Schroeder Van der Kolk on the origin of tubercle from changes in the epithelial cells of the air-vesicles.[2]

It would therefore appear, from what has now been stated, that the changes in the textural elements which lead to the formation of the corpuscles of pus, cancer, and tubercle, seem, up to a certain

[1] Rindfleisch, however, in a recent paper in Virchow's Archiv (vol. xxiv. p. 571), describes endogenous development in the tubercle-cells in a case of miliary tubercle of the base of the brain. He states that he has traced the development of the tubercle-cells in this case from the nuclei of the external coat of the arteries of the pia mater.

[2] Quoted in Paget's Lectures, vol. ii. p. 595.

time, to be the same, or that, so far as our means of observation enable us to determine, closely corresponding processes occur. Then, after reaching a certain stage, the resemblance between the processes ceases, and the corpuscles begin to assume their specific characters; although it not unfrequently happens that, after the development has apparently been completed, it is very difficult to decide, by a mere inspection, what is the nature of the corpuscles before us. But what it is that gives the specific characters to these corpuscles, I do not attempt to explain. It is still one of the mysteries of organization, and a satisfactory reply can only be given to it when the question, What is disease? is definitely answered.

But I trust that the necessarily brief review which we have now made over this very important department of pathology will be sufficient to show that the doctrine, that pathological cell-formations arise from pre-existing textural elements, has not been founded on insufficient data. And although I have far from exhausted all that might have been adduced in its support, yet enough, I think, has been brought forward to show that it is deserving of proper and careful consideration. Moreover, its universal applicability commends it to our notice. It explains the production of new formations, not in some merely, but in all the textures, and does not, like the exudation hypothesis, confessedly imperfect in the cases of inflammation of cartilage and the cornea, leave any residual quantities unaccounted for.

And to all this it may be added, that it is a doctrine based upon the most precise knowledge of the anatomy of the textures which has yet been attained. And, as daily observation teaches us, it is not until after a correct appreciation of the structure of a part has been acquired that we can hope to obtain an exact conception of the nature of the diseases to which it is liable. Every improvement, therefore, in our methods of anatomical investigation—every new fact added to our store of textural knowledge—gives precision to our pathological theories; and as years roll on, and fact is added to fact, we may in time, perhaps, be enabled to give a correct reply to the question, What is disease? and, still more importantly, to resolve the great problem of its effectual treatment.

PRINTED BY OLIVER AND BOYD, TWEEDDALE COURT, EDINBURGH.